Infant Growth Before and After Term: Effects on Neurodevelopment in Preterm Infants

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KEY WORDS

growth, motor development, cognitive development, preterm infants

ABBREVIATIONS

DINO—DHA for the Improvement of Neurodevelopmental Outcome
DHA—docosahexaenoic acid
BSID-II—Bayley Scales of Infant Development, 2nd Edition
MDI—Mental Development Index
PDI—Psychomotor Development Index
SGA—small for gestational age
WHO—World Health Organization
CI—confidence interval

Dr Belfort made substantial contributions to study design, data analysis, and interpretation of results and drafted the manuscript; Ms Rifas-Shiman made substantial contributions to data analysis and interpretation of results and critically revised the manuscript; Dr Sullivan made substantial contributions to data analysis and interpretation of results and critically revised the manuscript; Dr Collins made substantial contributions to interpretation of results and critically revised the manuscript; Dr McPhee obtained funding, made substantial contributions to interpretation of results, and critically revised the manuscript; Dr Ryan made substantial contributions to interpretation of results and critically revised the manuscript; Dr Kleinman made substantial contributions to data analysis and interpretation of results and critically revised the manuscript; Dr Gillman made substantial contributions to study design and data analysis and interpretation of results and critically revised the manuscript; Dr Gibson obtained funding, made substantial contributions to interpretation of results, and critically revised the manuscript; and Dr Makrides obtained funding, made substantial contributions to interpretation of results, and critically revised the manuscript. All authors approved the final version of the manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: Preterm infants are at risk for adverse neurodevelopmental outcomes. Greater weight gain before term (40 weeks' postmenstrual age) is associated with better outcomes. It is unclear to what extent growth after term affects neurodevelopment.

WHAT THIS STUDY ADDS: Weight and BMI gain to term were associated with better 18-month neurodevelopmental outcomes. After term, weight gain and linear growth were associated with better outcomes, but weight gain disproportionate to linear growth did not confer additional benefit.

abstract

OBJECTIVE: To identify sensitive periods of postnatal growth for preterm infants relative to neurodevelopment at 18 months' corrected age.

PATIENTS AND METHODS: We studied 613 infants born at <33 weeks' gestation who participated in the DHA for Improvement of Neurodevelopmental Outcome trial. We calculated linear slopes of growth in weight, length, BMI, and head circumference from 1 week of age to term (40 weeks' postmenstrual age), term to 4 months, and 4 to 12 months, and we estimated their associations with Bayley Scales of Infant Development, 2nd Edition, Mental (MDI) and Psychomotor (PDI) Development Indexes in linear regression.

RESULTS: The median gestational age was 30 (range: 2–33) weeks. Mean ± SD MDI was 94 ± 16, and PDI was 93 ± 16. From 1 week to term, greater weight gain (2.4 MDI points per *z* score [95% confidence interval (CI): 0.8–3.9]; 2.7 PDI points [95% CI: 1.2–.2]), BMI gain (1.7 MDI points [95% CI: 0.4–3.1]; 2.5 PDI points [95% CI: 1.2–3.9]), and head growth (1.4 MDI points [95% CI: −0.0–2.8]; 2.5 PDI points [95% CI: 1.2–3.9]) were associated with higher scores. From term to 4 months, greater weight gain (1.7 points [95% CI: 0.2–3.1]) and linear growth (2.0 points [95% CI: 0.7–3.2]), but not BMI gain, were associated with higher PDI. From 4 to 12 months, none of the growth measures was associated with MDI or PDI score.

CONCLUSIONS: In preterm infants, greater weight and BMI gain to term were associated with better neurodevelopmental outcomes. After term, greater weight gain was also associated with better outcomes, but increasing weight out of proportion to length did not confer additional benefit. *Pediatrics* 2011;128:e899–e906

More than 12% of infants in the United States are born preterm each year,[1] and the burden of neurodevelopmental disabilities in survivors of preterm birth is great.[2] Unfortunately, few strategies exist to improve these outcomes.

An important determinant of neurodevelopmental outcome for preterm infants is growth during NICU hospitalization. In a multicenter US cohort of 495 extremely low birth weight (<1000 g) infants, Ehrenkranz et al[3] showed that faster weight gain and head growth in the NICU were associated with higher cognitive and motor scores and a marked reduction in cerebral palsy at 18 to 22 months of age. The importance of NICU growth for optimizing brain development also is supported by results from a randomized trial of nutrient enriched preterm formula, in which both faster NICU weight gain and improved cognitive outcomes are demonstrated in infants[4] and school-aged[5] children who received the enriched preterm formula, compared with those who received the term formula.

Although considerable attention has been paid to growth during the NICU hospitalization, which typically occurs before term (40 weeks' postmenstrual age), in relation to later neurodevelopment, relatively little is known about the effect of growth after term. In 1 single-center study,[6] greater weight gain and linear growth in the first 2 years were associated with higher developmental scores at 2 years. Another study[7] revealed that adequate postnatal weight gain was particularly important for preterm infants with fetal growth restriction. In contrast, a relatively small ($n = 98$ in each group) randomized trial[8] of nutrient-enriched formula compared with standard formula for 9 months after NICU discharge revealed modestly faster weight gain and linear growth in infants who received the enriched formula, but no measureable improvement in cognitive or motor function at 18 months. A limitation of previous studies of postterm growth is a focus on wide time windows and thus an inability to pinpoint specific critical periods for growth with respect to later neurodevelopment in preterm infants. In addition, in few studies have interactions of growth been examined with other characteristics that make preterm infants more vulnerable to neurodevelopmental impairment, such as fetal growth restriction and social disadvantage; nor has any study assessed the effect of increasing adiposity as reflected by gain in weight-for-length.

A better understanding of the extent to which more rapid infant growth, both before and after term, affects neurodevelopment could help guide nutritional support therapy, with the ultimate goal of improving neurodevelopmental outcomes for this vulnerable population. In this study we aimed to (1) examine associations of weight gain, BMI (kg/m^2) gain, linear growth, and head growth in 3 time periods in the first year of life with neurodevelopmental outcome at 18 months' corrected age in a cohort of preterm infants born at <33 weeks' gestation and (2) examine the extent to which associations of growth with neurodevelopmental outcomes are stronger for infants more vulnerable to neurodevelopmental impairment.

PATIENTS AND METHODS

Study Design and Participants

We performed an observational analysis of data from the DHA for the Improvement of Neurodevelopmental Outcome (DINO) study, a randomized trial of docosahexaenoic acid (DHA) supplementation for preterm infants born at <33 weeks' gestation.[9] DHA is an n-3 long chain polyunsaturated fatty acid that has both structural and functional roles in the developing brain. Participants were recruited from 5 Australian perinatal centers from April 2001 to October 2005 and followed at term, 4, 12, and 18 months' corrected age. Details of recruitment and follow-up have been published.[9] The time points for evaluation were chosen because term is when the infants were due to be born, 4 months is typically the end of exclusive milk feeding, 12 months is the end of infancy, and 18 months is the standard age for neurodevelopmental assessment. Ethics approval was granted by the institutional review boards of each participating center. The main outcome of the DINO study was neurodevelopment at 18 months' corrected age as measured by the Bayley Scales of Infant Development, 2nd edition, (BSID-II). Of the 657 infants enrolled in the trial, for this analysis we included 613 (93%) participants with data for the BSID-II Mental Development Index (MDI) score at 18 months' corrected age, of whom 609 (99% of 613) had data for size at term, 599 (98%) had data for size at 4 months' corrected age, and 463 (76%) had data for size at 12 months' corrected age. The lower follow-up at 12 months was because that visit was optional for families. Children who did not follow up at 12 months had a similar mean birth weight and gestational age to those who did follow up (1320 vs 1318 g, $P = .99$; 29.3 vs 29.2 weeks, $P = .6$). Children were not excluded from this analysis because of blindness, deafness, or maternal substance abuse.

Compared with the 613 participants included in this analysis, the 44 participants we excluded had a lower mean birth weight (1181 vs 1318 g) and gestational age (28.2 vs 29.2 weeks). A higher proportion of excluded infants were male (61% vs 54%). Mothers of the excluded and included participants were similarly likely to have obtained a tertiary education (55% vs 50%), but mothers of excluded infants were less likely to be white (81% vs 91%).

Measurements

Infant Anthropometry

Infants were weighed and measured by trained DINO study staff weekly in the NICU until hospital discharge and at term, 4, 12, and 18 months' corrected age. Weight was measured to the nearest 5 g on a calibrated electronic scale. Length was measured to the nearest 0.1 cm using a recumbent length board. Head circumference was measured to the nearest 1 mm as the largest occipitofrontal circumference using a nonstretchable tape measure.

Neurodevelopment

The BSID-II was administered by trained psychologists or supervised psychology graduate students when participants were 18 months' corrected age. The BSID-II comprises 2 sub-scales: the MDI, which measures verbal and nonverbal cognition, and the Psychomotor Development Index (PDI), which incorporates both fine and gross motor skills. The BSID-II is scaled to a mean age-based score of 100 and an SD of 15, with a range of 50 to 150 points. Children who score <50 points are assigned a score of 45, and children who cannot be tested because of severe developmental delays are assigned a score of 40. For this study, the scaled score was calculated on the basis of the child's corrected age.

Covariates

DINO study staff collected data from the medical chart regarding gestational age, weekly intake of breast milk and formula, NICU diagnoses including intraventricular hemorrhage and chronic lung disease (defined as supplemental oxygen requirement at 36 weeks' corrected age), and exposure to postnatal steroids. Information about maternal smoking in pregnancy and parental education was obtained at study enrollment by maternal interview. At the 18 month follow-up visit, parents completed the Home Screening Questionnaire,[10] which measures aspects of the child's environment that promote cognitive development.

Statistical Analysis

We used mixed-effects regression models to estimate linear slopes representing weekly growth rates in weight, length, BMI, and head circumference from 1 week of age to term. We did not include the birth weight when estimating the slope because it includes a large amount of fluid weight lost in the first week of life. We then calculated internal *z* scores for growth rates for each measurement. For measurements at term, 4, 12, and 18 months' corrected age, we calculated *z* scores using World Health Organization standards[11] for birth, 4, 12, and 18 months chronologic age, respectively. For each measurement, to represent growth rate we calculated the *z* score change from term to 4 months and 4 to 12 months. We used a US reference[12] to calculate birth weight for gestational age *z* score, a measure of fetal growth.

To estimate associations of growth in each measurement in each time period with BSID-II scores, we used multivariable linear regression, adjusting for age, gender, gestational age, chronic lung disease, grade 3 or 4 intraventricular hemorrhage, postnatal steroids, breastfeeding status at discharge (never, weaned, mixed, exclusive), maternal age and education, smoking in pregnancy, paternal education, HSQ score, and DINO treatment arm. Because of the large number of multiple births (34% of participants were twins or triplets), we adjusted for clustering by shared mother; there were 503 mothers and 613 infants. We further adjusted the term to 4 month growth analyses for NICU growth and size at term in the same measurement. Similarly, we adjusted the 4 to 12 month growth analyses for NICU and term to 4-month growth, and size at 4 months.

To assess for effect modification, we performed analyses stratified by birth weight and fetal growth categories, gender, and maternal education level, hypothesizing that associations of postnatal growth with 18-month outcomes would be stronger for infants more vulnerable to neurodevelopmental impairment on the basis of lower birth weight, small for gestational age (SGA) status, male gender, or lower maternal education level. We defined SGA as birth weight at the <10th percentile for gestational age.[12] We used SAS 9.2 (SAS Institute Inc, Cary, NC) for all analyses.

RESULTS

Characteristics of study participants are shown in Table 1. In Fig 1 we show measures of infant size from term to 18 months' corrected age in *z* scores. A *z* score of 0 represents the mean for the World Health Organization (WHO) reference population. At term, mean *z* scores for weight, length, and BMI were <0, and at 4 months' corrected age, *z* scores for all measurements except length were even lower. By 12 months, the mean BMI *z* score was 0, which suggests that participants had, on average, caught up to the reference population in BMI. By 18 months, participants had additionally caught up in weight and length. Mean head circumference *z* score remained substantially above the mean for the reference population from term to 18 months.

Infant growth rates during the 3 time periods are shown in Table 2. From week 1 to term, mean weight gain was 211 g/week. Mean weight gain was slower from term to 4 months (176 g/week), and even slower from 4 to 12

TABLE 1 Characteristics of 613 DINO Participants and Their Mothers

Children	
Birth weight, median (range), kg	1.34 (0.32 to 2.62)
Gestational age, median (range), wk	30 (23 to 33)
Birth weight for gestational age *z* score, median (range)	−0.24 (−2.58 to 1.37)
Male, *n* (%)	328 (54)
Birth weight <1250 g, *n* (%)	272 (44)
SGA, *n* (%)[a]	54 (9)
Singleton, *n* (%)	404 (66)
Chronic lung disease, *n* (%)[b]	131 (21)
Intraventricular hemorrhage (grade 3 or 4), *n* (%)	20 (3)
Received postnatal steroids, *n* (%)	56 (9)
Breast milk-feeding status at discharge	
Exclusive, *n* (%)	323 (53)
Mixed, *n* (%)	121 (20)
Formula only, *n* (%)	168 (27)
Weaned, *n* (%)	0
Bayley scales of infant development at 18 mo	
MDI, mean (SD)	94 (16)
PDI, mean (SD)	93 (16)
Mothers	
Age, mean (SD), y	30.7 (5.5)
Received antenatal steroids, *n* (%)	540 (88)
Tertiary education, *n* (%)	306 (50)
Smoked in pregnancy, *n* (%)	152 (25)
Race/ethnicity, *n* (%)	
White	558 (91)
Asian	26 (4)
Aboriginal or other	29 (5)
Fathers/household	
Tertiary education, *n* (%)	270 (46)
Home-screening questionnaire score, mean (SD)	34.0 (3.6)

[a] Birth weight <10th percentile for gestational age.[12]
[b] Defined by supplemental oxygen requirement at 36 weeks' postmenstrual age.

TABLE 2 Weekly Growth Rates in First Year of Life

	Mean (Range)
Week 1 to term	
Weight, g	211 (77 to 411)
Length, cm	1.04 (0.71 to 1.42)
BMI, kg/m^2	0.59 (−0.40 to 0.43)
Head circumference, cm	0.89 (0.56 to 1.27)
Term to 4 mo	
Weight, g	176 (54 354)
Length, cm	0.74 (0.35 to 1.27)
BMI, kg/m^2	0.18 (−0.20 to 0.54)
Head circumference, cm	0.37 (0.12 to 0.89)
4 to 12 mo	
Weight, g	88 (19 to 271)
Length, cm	0.37 (0.16 to 1.49)
BMI, kg/m^2	0.01 (−0.16 to 0.23)
Head circumference, cm	0.13 (−0.09 to 0.48)

Term is 40 weeks' postmenstrual age. Other ages were corrected for prematurity.

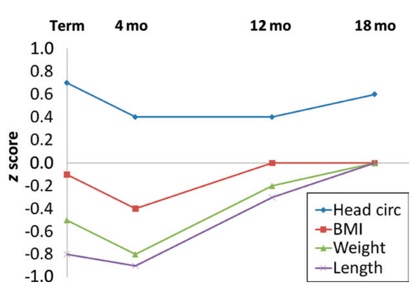

FIGURE 1
Infant size *z* scores from term to 18 months' corrected age. Mean weight and BMI are below the reference population at term and decline from term to 4 months but are equal to the WHO reference population by 18 months. Mean length *z* score is nearly 1 unit below the reference population at term and 4 months and is also equal to the reference population by 18 months. Head circumference remains above the reference population from term to 18 months.

months (88 g/week). We observed a similar slowing of growth rates in length, BMI, and head circumference.

In Table 3 adjusted associations of growth in weight, length, BMI, and head circumference in 3 time periods with 18-month BSID-II scores are shown. From week 1 to term, greater weight gain was associated with higher BSID-II scores, and we also observed associations for BMI gain and head growth during the same time period. Linear growth from 1 week to term was not associated with MDI or PDI scores. From term to 4 months, greater weight gain and linear growth were both associated with higher PDI scores, but BMI gain and head growth were not. We did not find any growth measurement from 4 to 12 months to be associated with BSID-II score.

Stratified analyses are shown in Tables 4 through 6. We observed stronger associations of weight and BMI gain from 1 week to term with MDI and PDI scores for lower (<1250 g) compared with higher (≥1250 g) birth weight infants. Comparing SGA infants with non-SGA infants, we observed markedly stronger associations of weight and BMI gain from 1 week to term with BSID-II scores for SGA infants, although confidence intervals were wide. We also observed stronger associations with MDI scores for infants of mothers with less than a tertiary education compared with a tertiary or greater education.

Regarding postterm growth, except linear growth from term to 4 months, which was positively associated with BSID-II for infants born at <1250 g but not ≥1250 g at birth, associations were similar between birth weight categories. For SGA but not non-SGA infants, BMI gain from 4 to 12 months was positively associated with MDI score. For infants born to mothers with less than a tertiary education, linear growth from term to 4 months and BMI gain from 4 to 12 months were positively associated with MDI scores, whereas those associations were not seen for infants of mothers with a tertiary education or greater. No substantial differences were seen in analyses stratified by gender (data not shown).

TABLE 3 Adjusted Associations of Infant Growth With 18-Month Bayley Scores

	Week 1 to Term (n = 561)[a]	Term to 4 mo[b] (n = 550)[a]	4 to 12 mo[c] (n = 432)[a]
MDI			
Weight gain	2.4 (0.8 to 3.9)	−0.4 (−1.9 to 1.1)	0.3 (−1.7 to 2.3)
Linear growth	0.3 (−1.0 to 1.7)	0.4 (−1.2 to 1.9)	−0.9 (−2.5 to 0.6)
BMI gain	1.7 (0.4 to 3.1)	−0.1 (−1.5 to 1.3)	0.8 (−0.8 to 2.4)
Head growth	1.4 (−0.0 to 2.8)	−0.5 (−2.2 to 1.1)	−0.0 (−1.7 to 1.6)
PDI			
Weight gain	2.7 (1.2 to 4.2)	1.7 (0.2 to 3.1)	0.1 (−1.9 to 2.0)
Linear growth	0.8 (−0.5 to 2.1)	2.0 (0.7 to 2.3)	0.3 (−1.1 to 1.6)
BMI gain	2.5 (1.2 to 3.9)	1.2 (−0.2 to 2.5)	0.9 (−0.8 to 2.6)
Head growth	2.5 (1.2 to 3.9)	0.2 (−1.3 to 1.8)	0.6 (−0.9 to 2.1)

Shown is the linear regression estimate of points per *z*-score increment (95% CI). Term is 40 weeks' postmenstrual age. Other ages were corrected for prematurity. All models were adjusted for age, gender, gestational age, NICU diagnoses (chronic lung disease, intraventricular hemorrhage grade 3 or 4), postnatal steroids, breastfeeding status at discharge, maternal age and education, smoking in pregnancy, paternal education, Home Screening Questionnaire score, and DINO treatment arm.

[a] Sample sizes are shown for weight models; numbers are slightly lower for length, BMI, and head circumference models.

[b] Also adjusted for size at term and NICU growth in the same measurement.

[c] Also adjusted for size at 4 months, NICU growth, and growth from term to 4 months in the same measurement.

DISCUSSION

In this large, multicenter cohort of infants born at <33 weeks' gestation, from week 1 of life to term, we found modest associations of greater weight and BMI gain and head growth with higher cognitive and motor scores at 18 months. From term to 4 months, we observed modest associations of greater weight gain and linear growth with higher motor scores, but increasing weight out of proportion to length was not associated with additional benefit. From 4 to 12 months, we did not identify associations of growth with neurodevelopmental outcomes at

TABLE 4 Adjusted Associations of Infant Growth With 18-Month Bayley Scores According to Birth Weight

	Week 1 to Term		Term to 4 mo[b]		4 to 12 mo[c]	
Birth weight	<1250 g (n = 249)[a]	≥1250 g (n = 312)[a]	<1250 g (n = 245)[a]	≥1250 g (n = 305)[a]	<1250 g (n = 187)[a]	≥1250 g (n = 245)[a]
MDI						
Weight gain	4.7 (2.1 to 7.4)	1.0 (−0.8 to 2.8)	−1.7 (−3.8 to 0.4)	0.2 (−1.6 to 1.9)	−2.7 (−5.8 to 0.5)	2.1 (−0.3 to 4.6)
Linear growth	0.5 (−1.4 to 2.5)	−0.0 (−1.9 to 1.8)	0.2 (−1.8 to 2.20)	−0.4 (−2.3 to 1.6)	−2.3 (−4.8 to 0.1)	0.5 (−1.4 to 2.4)
BMI gain	2.9 (1.0 to 4.8)	0.3 (−1.4 to 2.1)	−1.4 (−3.3 to 0.6)	0.8 (−0.8 to 2.3)	−0.7 (−3.0 to 1.7)	1.2 (−0.7 to 3.0)
Head growth	1.7 (−0.2 to 3.5)	0.4 (−1.6 to 2.4)	−0.7 (−3.1 to 1.8)	−0.8 (−2.9 to 1.3)	−1.3 (−4.1 to 1.5)	0.6 (−1.6 to 2.7)
PDI						
Weight gain	5.9 (3.2 to 8.6)	0.8 (−0.9 to 2.5)	0.9 (−1.0 to 2.8)	1.4 (−0.5 to 3.2)	−0.7 (−3.4 to 2.1)	0.3 (−1.9 to 2.6)
Linear growth	1.9 (0.1 to 3.7)	−0.3 (−2.0 to 1.4)	2.0 (0.2 to 3.7)	0.3 (−1.4 to 2.0)	0.1 (−1.7 to 1.9)	0.3 (−1.6 to 2.2)
BMI gain	4.2 (2.2 to 6.2)	0.6 (−1. to 2.3)	0.2 (−1.7 to 2.1)	0.7 (−1.9 to 3.2)	0.7 (−1.2 to 2.6)	1.1 (−1.3 to 3.6)
Head growth	3.0 (1.2 to 4.7)	0.9 (−1.2 to 3.1)	0.4 (−2.0 to 2.6)	−0.5 (−2.3 to 1.3)	0.5 (−1.6 to 2.6)	0.9 (−1.1 to 2.9)

Shown is the linear regression estimate of points per *z*-score increment (95% CI). Term is 40 weeks' postmenstrual age. Other ages were corrected for prematurity. SGA is birth weight at the <10th percentile for gestational age[12]. All models were adjusted for age, gender, gestational age, NICU diagnoses (chronic lung disease, intraventricular hemorrhage grade 3 or 4), postnatal steroids, breastfeeding status at discharge, maternal age and education, smoking in pregnancy, paternal education, Home Screening Questionnaire score, and DINO treatment arm.

[a] Sample sizes are shown for weight models; numbers are slightly lower for length, BMI, and head circumference models.

[b] Also adjusted for size at term and NICU growth in the same measurement.

[c] Also adjusted for size at 4 months, NICU growth, and growth from term to 4 months in the same measurement.

TABLE 5 Adjusted Associations of Infant Growth With 18-Month Bayley Scores According to Fetal Growth

	Week 1 to Term		Term to 4 mo[b]		4 to 12 mo[c]	
Fetal growth status	SGA (n = 50)[a]	Non-SGA (n = 511)[a]	SGA (n = 49)[a]	Non-SGA (n = 501)[a]	SGA (n = 38)[a]	Non-SGA (n = 394)[a]
MDI						
Weight gain	11.7 (4.5 to 18.8)	1.6 (0.0 to 3.3)	−4.4 (−9.7 to 0.9)	−0.2 (−1.7 to 1.3)	0.9 (−6.8 to 8.6)	0.2 (−1.9 to 2.2)
Linear growth	−1.5 (−5.8 to 2.8)	0.2 (−1.2 to 1.6)	2.2 (−1.8 to 6.2)	0.1 (−1.4 to 1.7)	−0.4 (−4.4 to 3.6)	−0.6 (−2.2 to 1.0)
BMI gain	9.2 (3.3 to 15.1)	1.0 (−0.3 to 2.3)	1.6 (−2.6 to 5.8)	0.0 (−1.2 to 1.3)	7.8 (3.2 to 12.4)	0.2 (−1.3 to 1.8)
Head growth	4.7 (−0.8 to 10.1)	1.0 (−0.5 to 2.4)	2.5 (−2.0 to 6.9)	−0.6 (−2.3 to 1.0)	−1.9 (−8.1 to 4.4)	0.1 (−1.6 to 1.7)
PDI						
Weight gain	11.2 (1.8 to 20.7)	1.9 (0.3 to 3.5)	−4.0 (−10.6 to 2.6)	1.8 (0.3 to 3.2)	0.9 (−8.6 to 10.4)	−0.0 (−2.1 to 2.0)
Linear growth	−0.8 (−5.1 to 3.6)	0.8 (−0.6 to 2.2)	2.4 (−1.6 to 6.3)	1.7 (0.4 to 3.0)	2.2 (−3.4 to 7.8)	0.5 (−0.9 to 2.0)
BMI gain	10.4 (4.3 to 16.5)	1.8 (0.4 to 3.2)	2.5 (−2.7 to 7.7)	1.2 (−0.1 to 2.5)	4.9 (−0.5, 10.2)	0.7 (−1.0 to 2.4)
Head growth	4.8 (−0.2 to 9.8)	2.4 (1.0 to 3.8)	1.9 (−2.9 to 6.6)	−0.1 (−1.61 to 1.5)	−3.2 (−10.7 to 4.4)	0.5 (−1.1 to 2.1)

Shown is the linear regression estimate of points per *z*-score increment (95% CI) and *P* value. Term is 40 weeks' postmenstrual age. Other ages were corrected for prematurity. SGA is birth weight at the <10th percentile for gestational age.[12] All models were adjusted for age, gender, gestational age, NICU diagnoses (chronic lung disease, intraventricular hemorrhage grade 3 or 4), postnatal steroids, breastfeeding status at discharge, maternal age and education, smoking in pregnancy, paternal education, Home Screening Questionnaire score, and DINO treatment arm.

[a] Sample sizes are shown for weight models; numbers are slightly lower for length, BMI, and head circumference models.

[b] Also adjusted for size at term and NICU growth in the same measurement.

[c] Also adjusted for size at 4mo, NICU growth, and growth from term to 4 months in the same measurement.

TABLE 6 Adjusted Associations of Infant Growth With 18-Month Bayley Scores According to Maternal Education

	Week 1 to Term		Term to 4 mo[b]		4 to 12 mo[c]	
Maternal education	<Tertiary (n = 276)[a]	≥Tertiary (n = 285)[a]	<Tertiary (n = 271)[a]	≥Tertiary (n = 279)[a]	<Tertiary (n = 183)[a]	≥Tertiary (n = 249)[a]
MDI						
Weight gain	3.7 (1.4 to 5.9)	1.4 (−0.8 to 3.7)	0.6 (−1.4 to 2.6)	−1.7 (−3.8 to 0.4)	0.4 (−2.5 to 3.3)	0.7 (−1.7 to 3.1)
Linear growth	1.0 (−1.0 to 3.0)	−0.1 (−2.1 to 1.9)	2.3 (0.1 to 4.4)	−2.0 (−4.0,−0.0)	−2.0 (−4.1 to 0.1)	−0.2 (−2.3 to 1.9)
BMI gain	2.5 (0.4 to 4.54)	1.2 (−0.62 to 3.0)	−0.2 (−2.3 to 1.9)	−0.3 (−2.0 to 1.4)	2.4 (−0.1 to 5.0)	0.1 (−1.7 to 1.9)
Head growth	2.8 (1.0 to 4.6)	0.2 (−1.9 to 2.3)	0.5 (−2.0 to 2.9)	−1.4 (−3.5 to 0.6)	−1.1 (−4.0 to 1.8)	0.2 (−1.7 to 2.1)
PDI						
Weight gain	4.5 (2.4 to 6.6)	0.9 (−1.2 to 3.0)	1.6 (−0.2 to 3.4)	1.3 (−0.7 to 3.4)	1.1 (−1.2 to 3.3)	−0.3 (−2.9 to 2.3)
Linear growth	2.5 (0.6 to 4.4)	−0.7 (−2.3 to 1.0)	2.0 (0.1 to 3.8)	1.9 (0.1 to 3.81)	−0.8 (−2.6 to 1.0)	0.6 (−1.1 to 2.3)
BMI gain	2.5 (0.5 to 4.5)	2.5 (0.7 to 4.2)	1.2 (−0.6 to 3.0)	0.9 (−0.9 to 2.6)	2.8 (0.4 to 5.2)	0.2 (−2.0 to 2.3)
Head growth	3.0 (1.1 to 5.0)	2.2 (0.4 to 4.0)	0.7 (−1.5 to 2.8)	−0.6 (−2.7 to 1.5)	−0.5 (−2.6 to 1.5)	0.6 (−1.4 to 2.6)

Shown is the linear regression estimate of points per z-score increment (95% CI) and P value. Term is 40 weeks' postmenstrual age. Other ages are corrected for prematurity. SGA is birth weight <10th percentile for gestational age.[12] All models were adjusted for age, gender, gestational age, NICU diagnoses (chronic lung disease, intraventricular hemorrhage grade 3 or 4), postnatal steroids, breastfeeding status at discharge, maternal age and education, smoking in pregnancy, paternal education, Home Screening Questionnaire score, and DINO treatment arm.

[a] Sample sizes are shown for weight models; numbers are slightly lower for length, BMI, and head circumference models.

[b] Also adjusted for size at term and NICU growth in the same measurement.

[c] Also adjusted for size at 4 months, NICU growth, and growth from term to 4 months in the same measurement.

18 months in the overall cohort, but for more vulnerable infants, including SGA infants and infants of less-educated mothers, we found positive associations of 4- to 12-month BMI gain with 18-month outcomes. Our results reveal that neurodevelopmentally sensitive periods for postnatal growth among preterm infants span time before and after the infant reaches term, and for the most vulnerable infants, extends through the end of the first year of life, a time when solid foods become a substantial part of the infant diet.

At least 2 previous studies of postnatal growth and later neurodevelopment in preterm infants spanned both the NICU hospitalization and the postdischarge period, but they did not subdivide this period. For example, 1 study[6] of very low birth weight (<1500 g) infants found that more rapid weight gain, linear growth, and head growth from birth to 2 years were associated with higher Bayley scores at 2 years. Another[13] found that larger head size at 8 months predicted higher school age IQ and academic achievement, independent of birth size. From those studies, one is unable to determine the relative importance of growth in the NICU, early infancy, or later infancy for neurodevelopment. In addition, those studies did not include measures of weight-for-length, such as BMI, which are critical for distinguishing weight gain that is proportional to as opposed to excessive for linear growth.

Our study is unique in that we examined growth both before term and in 2 time periods after term in the first year of life, and we included both linear growth and BMI gain. Like several previous studies,[3,4,14,15] our findings confirm that faster weight gain and head growth before 40 weeks' postmenstrual age ("term") is associated with better neurodevelopmental outcomes. We also found that increasing adiposity before term, reflected by BMI gain, was associated with better outcomes.

In contrast, little information exists regarding growth after term. In 1 study[16] of preterm, low birth weight (<2500 g) infants it was found that more rapid weight gain, linear growth, and head growth from term to 4 months, and weight-for-length and head growth from 4 to 12 months, were all associated with higher IQ at 8 years. Another[15] found that more rapid weight gain from discharge to 2 years was associated with better reading scores but not higher IQ. Those results contrast with ours in terms of cognitive outcomes, possibly because we examined infant outcomes, whereas those studies' outcomes were at school age. Also, infants in 1 study[16] were born in the 1980s, whereas we studied a contemporary cohort; it is possible that current postdischarge nutritional support is meeting the needs for cognitive development of more infants. We also found that weight gain and linear growth from term to 4 months were associated with improved 18-month motor outcomes. It is possible that the nutritional requirements to support optimal motor development are greater than for cognitive development. Another possibility is that poor feeding abilities are associated with slower weight gain and with poorer 18-month motor outcomes; we were not able to examine this possibility because we did not collect data about feeding behavior.

Assessing growth in multiple time periods is important biologically and clinically. Biologically, in every preterm newborn, the brain is still at the fetal stage of development,[17] during which processes such as dendritic and axonal growth and synaptogenesis predominate. In contrast, in late gestation and infancy, synaptic pruning and myelination become more prominent.[18] Clinically, timing matters because growth reflects different types of nutrition administered by different sets of health care providers. Much or all of the period before term is spent in the NICU, where infants typically receive parenteral nutrition followed by breast milk, and/or formula, which is given primarily by feeding tube. Nutrition is prescribed by the NICU care team. After term through the first year of life, parents and other caregivers feed infants breast milk and/or formula by mouth, as well as solid foods. In the United States, primary care pediatricians supervise nutritional care for most infants after NICU discharge. Designing interventions to improve neurodevelopmental outcomes through improved growth must target the correct time period, the main nutrition sources, the primary caregiver, and the relevant health care providers.

Although our results suggest that promoting faster weight gain and linear growth from term to 4 months may lead to better neurodevelopmental outcomes for preterm infants, it is also important to consider the potential risks of such a strategy. Rapidly increasing adiposity, indicated by gain in weight-for-length, in early infancy is associated with later overweight[19] and higher blood pressure.[20] Our finding that after term, weight gain and linear growth, but not BMI gain, were associated with better outcomes suggests that promoting excess adiposity would have no advantages because it may lead to later obesity and its consequences with no neurodevelopmental benefit.

Of note, the mean head circumference of our participants was substantially higher than the mean for the WHO reference population from term to 12 months of age. Although the reason for this difference is unclear, our finding is supported by a recent report[21] that the WHO standard tended to overestimate the proportion of infants with microcephaly in a large US primary care network.

Strengths of our study include a multicenter sample of preterm infants and detailed growth data both before and after term. Generalizability of our findings may be limited somewhat by the relatively high socioeconomic status of our participants, although we performed analyses stratified by maternal education. We were able to adjust our analyses for many important confounders related to severity of illness, specific medical complications of prematurity and NICU treatments, and social factors such as maternal education, household income, and the home environment, but results from observational studies such as this one are subject to residual confounding by unmeasured factors. Although the BSID-II is a well accepted neurodevelopmental outcome measure for preterm infants, it is a relatively poor predictor of later outcomes,[22] does not provide information about specific cognitive processes such as memory or attention,[23] and does not reflect higher level cognitive functions that develop later in childhood.

CONCLUSIONS

Before term, increasing adiposity as reflected by weight and BMI gain were associated with better neurodevelopmental outcomes; in contrast, from term to 4 months, increasing weight out of proportion to length was not associated with additional benefit. Strategies to increase BMI gain before term, and to increase length but not excess weight from term to 4 months, may improve neurodevelopmental outcomes for preterm infants. Our findings of a larger benefit among infants born small or to mothers with less education reveal that additional attention and support may be warranted for infants who are more vulnerable to neurodevelopmental impairment.

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